Skeletal Muscle Relaxants
Therapeutic Class Review (TCR)

December 3, 2012

The literature review is current through March 11, 2016.

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
baclofen (Lioresal®)[1]	generic	For the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms, concomitant pain, clonus, and muscular rigidity
carisoprodol (Soma®)[2]*	generic	As an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions
carisoprodol compound or carisoprodol and aspirin[3]*	generic	
chlorzoxazone[4] (Parafon Forte® DSC)	generic	
chlorzoxazone[5] (Lorzone™)	generic	
cyclobenzaprine (Flexeril®)[6]	generic	
Cyclobenzaprine (Fexmid®)[7]	generic	
cyclobenzaprine ER (Amrix®)[8]	generic	
dantrolene sodium (Dantrium®)[9†]	generic	For the control of clinical spasticity resulting from upper motor neuron disorders such as spinal cord injury, stroke, cerebral palsy, or multiple sclerosis
metaxalone (Skelaxin®)[10]	generic	As an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions
methocarbamol (Robaxin®)[11]	generic	
orphenadrine citrate[12]	generic	
orphenadrine compound or orphenadrine/aspirin/ caffeine[13]	generic	
tizanidine (Zanaflex®)[14]	generic	For the acute and intermittent management of increased muscle tone associated with spasticity

* Products containing carisoprodol are Schedule IV controlled substances.

† Oral Dantrium is also indicated preoperatively to prevent or attenuate the development of signs of malignant hyperthermia in known, or strongly suspect, malignant hyperthermia susceptible patients who require anesthesia and/or surgery.

OVERVIEW

Skeletal muscle relaxants are Food and Drug Administration (FDA)-approved to treat 2 different types of conditions: muscular pain or spasms from peripheral musculoskeletal conditions and spasticity from upper motor neuron syndromes. Both conditions affect patients' mobility and affect independence in activities of daily living and work.

Spasticity is a condition in which muscles are continuously contracted causing stiffness or tightness which may interfere with movement and speech. It is usually caused by damage to the portion of the brain or spinal cord that controls voluntary movement. Spasticity is a major health concern and can be associated with a number of disease entities, such as spinal cord injury, multiple sclerosis, traumatic brain injury, cerebral palsy, and stroke. Symptoms may include hypertonicity, clonus, exaggerated deep tendon reflexes, muscle spasms, scissoring, and fixed joints. The degree of spasticity varies from mild muscle stiffness to severe, painful, and uncontrollable muscle spasms. Spasticity may cause decreased range of motion, contractures, sleep disorders, and impaired ambulation.

Common musculoskeletal conditions associated with muscle spasms include low back pain, neck pain, tension headaches, and myofascial pain syndrome. Hypertonicity and hyperreflexia are not present as with upper motor neuron syndromes. These conditions can cause significant disability and pain.

The 2005 Multiple Sclerosis Council for Clinical Practice Guidelines for spasticity management in multiple sclerosis included the oral skeletal muscle relaxant agents baclofen and tizanidine as effective first-line treatment options.[15] Generally, skeletal muscle relaxants are administered orally. Baclofen can be administered intrathecally, and orphenadrine can be administered either intravenously (IV) or intramuscularly (IM). Only the oral agents are included in this review.

PHARMACOLOGY

Drug	Mechanism of Action
baclofen (Lioresal)[16]	▪ Inhibits monosynaptic and polysynaptic reflexes at the spinal level by hyperpolarization of afferent terminals ▪ Additionally acts at supraspinal sites ▪ Has general CNS depressant properties
carisoprodol (Soma)[17]	▪ In animals, it produces muscle relaxation by blocking interneuronal activity in the descending reticular formation and spinal cord.
carisoprodol compound or carisoprodol and aspirin[18]	▪ Carisoprodol, in animals, produces muscle relaxation by blocking interneuronal activity in the descending reticular formation and spinal cord. ▪ Aspirin is a non-narcotic analgesic with anti-inflammatory activity. Inhibition of prostaglandin biosynthesis appears to account for most of its anti-inflammatory and for at least part of its analgesic properties.
chlorzoxazone[19, 20]	▪ Acts primarily at the spinal cord level and subcortical areas of the brain, inhibiting multisynaptic reflex arcs involved in producing and maintaining skeletal muscle spasm of varied etiology
cyclobenzaprine (Flexeril, Fexmid)[21, 22] cyclobenzaprine ER (Amrix)[23]	▪ Relieves skeletal muscle spasm of local origin without interfering with muscle function ▪ Ineffective in muscle spasm due to CNS disease
dantrolene sodium (Dantrium)[24]	▪ In isolated nerve-muscle preparation, dantrolene produced relaxation by affecting contractile response of the skeletal muscle at a site beyond the myoneural junction and directly on the muscle itself. ▪ In skeletal muscle, dantrolene dissociates the excitation-contraction coupling, probably by interfering with the release of calcium from the sarcoplasmic reticulum. ▪ Does not appear to directly affect the CNS; the extent of its indirect effect is unknown.
metaxalone (Skelaxin)[25] methocarbamol (Robaxin)[26]	▪ May be caused by general CNS depression ▪ The drug has no direct action on the contractile mechanism of striated muscle, the motor endplate, or the nerve fiber.
orphenadrine citrate[27]	▪ Acts centrally at the brain stem ▪ Does not directly relax tense skeletal muscles ▪ Possesses anticholinergic actions
orphenadrine compound or orphenadrine/aspirin/ caffeine[28]	▪ Orphenadrine acts centrally at the brain stem. ▪ Orphenadrine does not directly relax tense skeletal muscles. ▪ Orphenadrine possesses anticholinergic actions. ▪ Aspirin is a non-narcotic analgesic with anti-inflammatory activity. Inhibition of prostaglandin biosynthesis appears to account for most of its anti-inflammatory and for at least part of its analgesic properties. ▪ Caffeine increases levels of intracellular cyclic-AMP.
tizanidine (Zanaflex)[29]	▪ Agonist at alpha$_2$-adrenergic receptor sites ▪ Reduces spasticity by increasing presynaptic inhibition of motor neurons

PHARMACOKINETICS

Drug	Half-Life (hours)	Metabolites	Major Route of Elimination
baclofen (Lioresal)[30]	2 - 4	--	kidney
carisoprodol (Soma)[31]	2 (carisoprodol) 10 (meprobamate)	meprobamate	liver
carisoprodol/ aspirin[32]	2 (carisoprodol) 2-4 (salicylic acid)	meprobamate salicylic acid	kidney and liver
chlorzoxazone (Parafon Forte DSC, Lorzone) [33, 34]	1	--	kidney
cyclobenzaprine (Flexeril, Fexmid)[35, 36]	18	several metabolites	kidney
cyclobenzaprine ER (Amrix)[37]	32	--	kidney
dantrolene sodium (Dantrium)[38]	8.7	5-hydroxy dantrolene acetylamino	kidney
metaxalone (Skelaxin)[39]	8-9	--	kidney
methocarbamol (Robaxin)[40]	1-2	--	kidney
orphenadrine citrate[41]	14-16 (orphenadrine) 2-25 (8 metabolites)	8 metabolites	kidney
orphenadrine/ aspirin/caffeine[42]	15.5 2-4 (salicylic acid) 3-7 hours (several metabolites)	--	kidney liver and kidney
tizanidine (Zanaflex)[43]	2.5	--	kidney

CONTRAINDICATIONS/WARNINGS

Dantrolene (Dantrium) labeling has a black box warning regarding a potential for hepatotoxicity.[44] The incidence of symptomatic hepatitis (fatal and nonfatal) reported in patients taking up to 400 mg per day is much lower than in those taking $\geq$ 800 mg per day. Even sporadic short courses of the higher dose levels within a treatment regimen markedly increased the risk of serious hepatic injury. Liver dysfunction, as evidenced by liver enzyme elevations, has been observed in patients exposed to the drug for varying periods of time. Overt hepatitis has been most frequently observed between the 3rd and 12th months of therapy. Risk of hepatic injury appears to be greater in females, in patients >35 years of age, and in patients taking other medications in addition to dantrolene. If no observable benefit is derived from therapy after 45 days, discontinue use.

Dantrolene is not for use where spasticity is utilized to sustain upright balance/posture in ambulation or when spasticity is utilized to obtain or maintain increased function.

Baclofen (Lioresal) should be reduced slowly when discontinuing, as hallucinations and seizures have occurred on abrupt withdrawal of the drug.[45] In patients with epilepsy, the clinical state and electroencephalogram (EEG) should be monitored at regular intervals, since deterioration in seizure control and EEG have been reported occasionally in patients taking baclofen.

Carisoprodol-containing products are contraindicated in patients with a history of acute intermittent porphyria.[46] The active metabolite of carisoprodol is meprobamate, a controlled substance. Post-marketing cases of dependence, withdrawal, and abuse have been reported with prolonged usage. Carisoprodol has sedative effects which may impair the mental and/or physical abilities needed for the performance of potentially hazardous tasks, and there have been post-marketing reports of motor vehicle accidents associated with its use.[47]

Rare but serious hepatocellular toxicity has been reported with the use of chlorzoxazone.[48,49]

Cyclobenzaprine (Flexeril, Fexmid, Amrix) is contraindicated in patients with hyperthyroidism, congestive heart failure, during the acute recovery phase of myocardial infarction, and in patients with arrhythmias and heart block conduction disturbances. Incidences of hyperpyretic crisis seizures and deaths have occurred in patients receiving cyclobenzaprine concomitantly with monoamine oxidase (MAO) inhibitors. Use of cyclobenzaprine in patients with moderate to severe hepatic function impairment is not recommended.[50] Cyclobenzaprine ER capsules (Amrix) should not be used in the elderly or in patients with hepatic impairment. Because of its atropine-like action, use cyclobenzaprine with caution in patients with a history of urinary retention, angle-closure glaucoma or increased intraocular pressure, and in patients taking anticholinergic medication. Serotonin syndrome has been reported in patients using cyclobenzaprine in combination with other serotonergic medications (e.g., tramadol, MAO inhibitors, serotonin reuptake inhibitors).[51]

Metaxalone (Skelaxin) is contraindicated in drug-induced, hemolytic, or other anemias, and in significantly impaired renal or hepatic function.[52]

Orphenadrine-containing products are contraindicated in patients with glaucoma, pyloric or duodenal obstruction, stenosing peptic ulcers, prostatic hypertrophy or obstruction of the bladder neck, and myasthenia gravis.[53]

Aspirin is contraindicated in patients who are hypersensitive to salicylates or nonsteroidal anti-inflammatory drugs (NSAIDs), children or teenagers with influenza, chickenpox, or an acute febrile illness due to possible development of Reye's syndrome, and bleeding disorders.[54] Aspirin is also contraindicated in patients with a serious GI complication (e.g., bleeding, perforations, obstruction) due to aspirin use or aspirin-induced asthma.[55]

Tizanidine (Zanaflex) is primarily metabolized by CYP1A2; therefore, concomitant use with ciprofloxacin (Cipro®) or fluvoxamine is contraindicated.[56] Tizanidine occasionally causes liver injury, most often hepatocellular in type. In controlled clinical studies, approximately 5% of patients treated with tizanidine had elevations of liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) to greater than 3 times the upper limit of normal (or 2 times if baseline levels were elevated), compared with 0.4% in control patients. Most cases resolved rapidly upon drug withdrawal, with no reported residual problems. Tizanidine use has been associated with hallucinations. Upon discontinuation, especially in patients who have been receiving high doses for long periods, decrease the dose slowly to minimize the risk of withdrawal and rebound hypertension, tachycardia, and hypertonia.

DRUG INTERACTIONS

Caution should be used with all skeletal muscle relaxants and other CNS depressants, barbiturates, and alcohol since the sedative effects may be additive.

Cyclobenzaprine (Flexeril, Fexmid, Amrix) may have life-threatening interactions with MAO inhibitors. MAO inhibitors should be discontinued at least 14 days before starting cyclobenzaprine. Cyclobenzaprine may enhance the seizure risk in patients taking tramadol.[57]

Concomitant use of carisoprodol-containing products with CYP2C19 inhibitors, omeprazole, or fluvoxamine (Luvox®, Luvox® CR), may increase carisoprodol levels and decrease those of the active metabolite, meprobamate. The impact of these drug interactions is unknown. Co-administration of CYP2C19 inducers, such as rifampin or St. John's wort, with carisoprodol-containing products could result in decreased exposure of carisoprodol and increased exposure of meprobamate.[58]

While a definite drug interaction has not yet been established, caution should be observed if dantrolene is given concomitantly with estrogen. Hepatotoxicity has occurred more often in women over 35 years of age receiving concomitant estrogen therapy. Also, plasma protein binding of dantrolene may be reduced in patients taking warfarin.[59]

Methocarbamol may inhibit the effect of pyridostigmine bromide. Use with caution in patients with myasthenia gravis receiving anticholinesterase agents.[60]

Concurrent use of orphenadrine and amantadine has been shown to increase the effect of amantadine. Therapeutic effects of haloperidol and phenothiazines have been decreased with the use of orphenadrine.

Concomitant use of tizanidine with fluvoxamine or ciprofloxacin, potent inhibitors of CYP1A2, is contraindicated due to significant alterations of pharmacokinetic parameters of tizanidine including increased AUC, half-life, Cmax, increased oral bioavailability, and decreased plasma clearance. Because of potential drug interactions, concomitant use of tizanidine with other CYP1A2 inhibitors, such as zileuton, other fluoroquinolones, antiarrhythmic agents (amiodarone, mexiletine, propafenone, and verapamil), cimetidine, famotidine, acyclovir, and ticlopidine should be avoided. Retrospective analysis of population pharmacokinetic data following single and multiple dose administration of 4 mg tizanidine, however, showed that women concurrently taking oral contraceptives had 50% lower clearance of tizanidine compared to women not on oral contraceptives.[61]

ADVERSE EFFECTS

All skeletal muscle relaxants have a similar adverse effect profile with somnolence, dizziness, dry mouth, and asthenia being some of the most commonly reported effects. Each individual agent may also have additional adverse events based on its structure and mechanism of action.

Drug	Asthenia (%)	Dizziness (%)	Dry Mouth (%)	Somnolence (%)
baclofen (Lioresal)[62]	5-15	5-15	reported	10-63
carisoprodol (Soma)[63]	nr	7-8	nr	13-17
carisoprodol / aspirin[64]	nr	reported	nr	reported
chlorzoxazone (Parafon Forte DSC, Lorzone)[65, 66]	nr	reported	nr	reported
Cyclobenzaprine (Flexeril, Fexmid)[67, 68]	reported	19	21-32	39
cyclobenzaprine ER (Amrix)[69]	reported	3-6	6-14	1-2
dantrolene (Dantrium)[70]	reported	reported	nr	reported
metaxalone (Skelaxin)[71]	nr	reported	nr	reported
methocarbamol (Robaxin)[72]	reported	reported	nr	reported
orphenadrine citrate[73]	nr	reported	nr	reported
orphenadrine / aspirin / caffeine[74]	nr	reported	nr	reported
tizanidine (Zanaflex)[75]	78	16-45	88	92

Adverse effects data are obtained from product package information and, therefore, should not be considered comparative or all inclusive. nr = not reported

Tizanidine (Zanaflex) had a 5% incidence in clinical trials of causing increased liver enzymes 3 times the upper limit of normal.[76] There have also been 3 deaths from hepatocellular injury in post-marketing reports.

SPECIAL POPULATIONS[77]

Pediatrics

Safety and efficacy of carisoprodol-containing products and oral methocarbamol (Robaxin) in pediatric patients less than 16 years of age have not been established.[78,79]

Safety and efficacy of cyclobenzaprine (Flexeril, Fexmid) in pediatric patients less than 15 years of age have not been established.[80,81]

Metaxalone (Skelaxin) and baclofen (Lioresal) use in pediatric patients less than 12 years of age have not been established.[82,83]

Safety and efficacy of dantrolene sodium (Dantrium) in pediatric patients less than 5 years of age have not been established.[84]

There are no well-controlled studies of safety and efficacy of tizanidine (Zanaflex), cyclobenzaprine ER (Amrix), chlorzoxazone, or orphenadrine-containing products in children.[85]

Aspirin-containing products are contraindicated in children or teenagers with influenza, chickenpox, or an acute febrile illness due to possible development of Reye's syndrome.[86]

Pregnancy

Cyclobenzaprine is Pregnancy Category B while baclofen, carisoprodol, chlorzoxazone, dantrolene, orphenadrine, and tizanidine are Pregnancy Category C.[87,88,89]

Safety of metaxalone has not been established with regard to possible adverse reactions on fetal development.[90]

Aspirin is Pregnancy Category D. Avoid aspirin use 1 week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.

DOSAGES

Drug	Initial Dose	Maximum Daily Dose	Availability
baclofen (Lioresal)[91]	5 mg 3 times daily; may be increased by 5 mg/dose every 3 days as needed to a max of 80 mg/day	80 mg	10, 20 mg tablets
carisoprodol (Soma)*[92]	250 mg to 350 mg 3 or 4 times daily; take the last dose at bedtime	1,400 mg	250, 350 mg tablets
carisoprodol / aspirin *[93]	200 mg/325 mg 4 times daily	1,600 mg/ 2,600 mg	200/325 mg tablets
chlorzoxazone (Parafon Forte DSC, Lorzone)[94, 95]	250 mg to 750 mg 3 or 4 times daily (generic, Parafon Forte DSC) 375 mg to 750 mg 3 or 4 times daily (Lorzone)	750 mg 3 or 4 times daily	500 mg tablets (generic, Parafon Forte DSC) 375, 750mg (Lorzone)
cyclobenzaprine (Flexeril)*[96]	5 mg 3 times daily; may increase to 10 mg 3 times daily	30 mg	5, 10 mg tablets
cyclobenzaprine (Fexmid)[97]	7.5 mg 3 times daily	--	7.5 mg tablet
cyclobenzaprine ER (Amrix)*[98]	15 mg daily; may increase to 30 mg daily	--	15, 30 mg capsules
dantrolene (Dantrium)[99]	Initial dose 25 mg every day; increase at 4 to 7 day intervals to 25 mg twice daily to 4 times daily, up to max 100 mg twice daily to 4 times daily, if necessary. Maintain each dosage level for 4 to 7 days to determine response.	400 mg	25, 50, 100 mg capsules
metaxalone (Skelaxin)[100]	800 mg 3 or 4 times daily	--	400 (generic only), 800 mg tablet
methocarbamol (Robaxin)[101]	methocarbamol 500 mg tablets: Initial dosage: 3 tablets 4 times a day. Maintenance dosage: 2 tablets 4 times a day. methocarbamol 750 mg tablets: Initial dosage: 2 tablets 4 times a day. Maintenance dosage: 1 tablet every 4 hours or 2 tablets 3 times a day.	8 g	500, 750 mg tablets
orphenadrine citrate[102]	100 mg twice daily	--	100 mg ER tablets
orphenadrine / aspirin / caffeine[103]	low strength: 1 to 2 tablets 3 to 4 times daily high strength: a half or whole tablet 3 to 4 times daily	--	orphenadrine/aspirin/ caffeine: 25/385/30 mg tablets
tizanidine (Zanaflex)[104]	4 mg daily; increase dose by 2-4 mg gradually; repeat dose every 6 to 8 hours. Target dose is 8 mg 3 times daily.	36 mg	2, 4 mg tablets 2, 4, 6 mg capsules

*Recommended for short-term usage (2 to 4 weeks) because of the lack of evidence of effectiveness for long-term usage.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials published in the last 20 years are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Two consistent limitations appear throughout the controlled studies that have been conducted: the lack of quantitative and sensitive functional assessment and the lack of comparative trials between different agents.[105] In the majority of trials in which meaningful functional assessment was included, the study drug failed to improve function, even though the antispastic action was significant. Placebo-controlled trials of virtually all major centrally acting antispastic agents have shown that sedation, reduction of global performance, and muscle weakness are frequent adverse effects.

The literature review of significant trials comparing agents within this therapeutic class is complete as of March 11, 2016. Only published comparative studies are included below.

tizanidine (Zanaflex) and baclofen (Lioresal)

An early double-blind trial compared tizanidine with baclofen in 40 patients with severe disabilities related to multiple sclerosis.[106] Patients were randomized to either treatment for 6 weeks. The mean dose was 23 mg for tizanidine and 59 mg for baclofen. Similar antispastic effects were observed between the 2 treatments. Adverse effects of both drugs included sleepiness, muscular weakness, and dry mouth. Sudden discontinuations of either drug resulted in a transient increase in spasticity in approximately half of the patients.

A double-blind study enrolled 100 patients with multiple sclerosis with chronic spasticity to compare the effectiveness of tizanidine and baclofen.[107] Patients were randomized to daily doses of tizanidine 6 mg or baclofen 15 mg. Doses were titrated upward during the first 2 weeks of therapy to a daily maximum of tizanidine 24 mg or baclofen 60 mg. Optimal doses were administered for 6 weeks. Efficacy and tolerability were evaluated after 2 and 8 weeks. Both drugs improved functional status of patients in 80% (tizanidine) and 76% (baclofen) of patients (p=NS). The antispastic efficacy of tizanidine was greater after 8 weeks than after 2 weeks, whereas the efficacy of baclofen decreased slightly with time. Both drugs showed good overall tolerability in more than 60% of patients.

Thirty patients with spasticity due to cerebrovascular lesions were enrolled in a double-blind study to compare the efficacy and tolerability of tizanidine and baclofen.[108] Titration occurred over a 2-week period for each patient. Maximum doses were tizanidine 20 mg per day and baclofen 50 mg per day.

Efficacy and tolerability were assessed monthly, initially, then bi-monthly during the 50-week maintenance phase. Both drugs improved the symptoms of spasticity with 87% of patients showing an improvement in excessive muscle tone ($p<0.01$) in the tizanidine group and 79% of patients in the baclofen group ($p<0.01$). Adverse effects were mild and transient with tizanidine, and no patients discontinued therapy. Three patients discontinued baclofen due to severe adverse effects. There were no statistically significant differences between the 2 drugs.

META-ANALYSIS

A comprehensive comparative systematic review of the skeletal muscle relaxants was completed in 2004.[109] A total of 101 randomized trials were included from MEDLINE, Cochrane Library, and Embase searches through January 2003. The purpose of the meta-analysis was to determine if there was evidence that 1 or more skeletal muscle relaxants is superior to others in efficacy or safety. Of all the randomized trials, none were rated good quality; all studies were poor to fair quality. Populations included adults and pediatric patients with spasticity or a musculoskeletal syndrome. It included the following oral drugs classified as skeletal muscle relaxants: baclofen, carisoprodol (Soma), chlorzoxazone, cyclobenzaprine, dantrolene (Dantrium), metaxalone (Skelaxin), methocarbamol (Robaxin), orphenadrine, and tizanidine (Zanaflex). There is fair evidence that baclofen, tizanidine, and dantrolene are effective compared to placebo in patients with spasticity (primarily multiple sclerosis). There is fair evidence that baclofen and tizanidine are roughly equivalent for efficacy in patients with spasticity, but insufficient evidence to determine the efficacy of dantrolene compared to baclofen or tizanidine. Also, fair evidence supports that the overall rate of adverse effects between tizanidine and baclofen are similar. However, tizanidine is associated with more dry mouth, and baclofen is associated with more weakness. Furthermore, there is fair evidence that cyclobenzaprine, carisoprodol, orphenadrine, and tizanidine are effective compared to placebo in patients with musculoskeletal conditions (primarily acute back or neck pain). The review concluded that there was insufficient evidence to determine the relative efficacy or safety of cyclobenzaprine, carisoprodol, orphenadrine, tizanidine, metaxalone, methocarbamol, and chlorzoxazone.

SUMMARY

Skeletal muscle relaxants consist of antispasticity and antispasmodic agents, a distinction often overlooked. The antispasticity agents, such as baclofen, tizanidine, and dantrolene, aid in reducing muscle hypertonicity and involuntary jerks. Antispasmodic agents, such as carisoprodol, cyclobenzaprine, metaxalone, and methocarbamol, are primarily used to treat musculoskeletal conditions.

Very few comparative studies are available for the skeletal muscle relaxants. Studies are generally not considered of good quality. Overall, there are not enough data to support that the skeletal muscle relaxants have different efficacy or safety. For these agents, the efficacy of the skeletal muscle relaxants is often impacted by the level of adverse effects; therefore, agents must be titrated to produce acceptable benefits while minimizing adverse effects.

REFERENCES

1 Lioresal [package insert]. East Hanover, NJ; Novartis; April 1998.
2 Soma [package insert]. Somerset, NJ; Meda Pharmaceuticals; October 2009.
3 Carisoprodol compound. online.factsandcomparisons.com. Accessed on November 28, 2012.
4 Parafon forte [package insert].Raritan, NJ; Ortho McNeil; August 2000.
5 Lorzone [package insert]. Sayreville NJ; Vertical Pharma; October 2010.
6 Flexeril [package insert]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/017821s045lbl.pdf. Accessed on November 30, 2012.
7 Fexmid. [package insert]. San Diego, CA; Victory Pharmaceuticals; October 2007.
8 Amrix [package insert]. Frazer, PA; Cephalon; December 2008.
9 Dantrium [package insert]. Rochester, MI; JHP Pharmaceuticals; August 2008.
10 Skelaxin [package insert]. Bristol, TN; King Pharmaceuticals; April 2008.
11 Robaxin [package insert]. Milwaukee, WI; Schwarz Pharma; February 2003.
12 Orphenadrine. online.factsandcomparisons.com. Accessed on December 16, 2011.
13 Orphenadrine compound. online.factsandcomparisons.com. Accessed on November 28, 2012.
14 Zanaflex [package insert]. Hawthorne, NY; Acorda Therapeutics; April 2008.
15 Haselkorn JK, Little JW, et al. Spasticity Management in Multiple Sclerosis: Evidence-Based Management Strategies for Spasticity Treatment in Multiple Sclerosis. J. Spinal Cord Medicine. 2005; 28(2).
16 Lioresal [package insert]. East Hanover, NJ; Novartis; April 1998.
17 Soma [package insert]. Somerset, NJ; Meda Pharmaceuticals; October 2009.
18 Carisoprodol compound. online.factsandcomparisons.com. Accessed on November 28, 2012.
19 Parafon forte [package insert].Raritan, NJ; Ortho McNeil; August 2000.
20 Lorzone [package insert]. Sayreville NJ; Vertical Pharma; October 2010.
21 Flexeril [package insert]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/017821s045lbl.pdf. Accessed on November 30, 2012.
22 Fexmid. [package insert]. San Diego, CA; Victory Pharmaceuticals; October 2007.
23 Amrix [package insert]. Frazer, PA; Cephalon; December 2008.
24 Dantrium [package insert]. Rochester, MI; JHP Pharmaceuticals; August 2008.
25 Skelaxin [package insert]. Bristol, TN; King Pharmaceuticals; April 2008.
26 Robaxin [package insert]. Milwaukee, WI; Schwarz Pharma; February 2003.
27 Orphenadrine. online.factsandcomparisons.com. Accessed on November 28, 2012.
28 Orphenadrine compound. online.factsandcomparisons.com. Accessed on November 28, 2012.
29 Zanaflex [package insert]. Hawthorne, NY; Acorda Therapeutics; April 2008.
30 Lioresal [package insert]. East Hanover, NJ; Novartis; April 1998.
31 Soma [package insert]. Somerset, NJ; Meda Pharmaceuticals; October 2009.
32 Carisoprodol compound. online.factsandcomparisons.com. Accessed on November 28, 2012.
33 Parafon forte [package insert].Raritan, NJ; Ortho McNeil; August 2000.
34 Lorzone [package insert]. Sayreville NJ; Vertical Pharma; October 2010.
35 Flexeril [package insert]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/017821s045lbl.pdf. Accessed on November 30, 2012.
36 Fexmid. [package insert]. San Diego, CA; Victory Pharmaceuticals; October 2007.
37 Amrix [package insert]. Frazer, PA; Cephalon; December 2008.
38 Dantrium [package insert]. Rochester, MI; JHP Pharmaceuticals; August 2008.
39 Skelaxin [package insert]. Bristol, TN; King Pharmaceuticals; April 2008.
40 Robaxin [package insert]. Milwaukee, WI; Schwarz Pharma; February 2003.
41 Orphenadrine, online.factsandcomparisons.com. Accessed on November 28, 2012.
42 Orphenadrine compound. online.factsandcomparisons.com. Accessed on November 28, 2012.
43 Zanaflex [package insert]. Hawthorne, NY; Acorda Therapeutics; April 2008.
44 Dantrium [package insert]. Rochester, MI; JHP Pharmaceuticals; August 2008.
45 Lioresal [package insert]. East Hanover, NJ; Novartis; April 1998.
46 Soma [package insert]. Somerset, NJ; Meda Pharmaceuticals; October 2009.
47 Soma [package insert]. Somerset, NJ; Meda Pharmaceuticals; October 2009.
48 Parafon forte [package insert].Raritan, NJ; Ortho McNeil; August 2000.
49 Lorzone [package insert]. Sayreville NJ; Vertical Pharma; October 2010.
50 Flexeril [package insert]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/017821s045lbl.pdf. Accessed on November 30, 2012.
51 Amrix [package insert]. Frazer, PA; Cephalon; December 2008.
52 Skelaxin [package insert]. Bristol, TN; King Pharmaceuticals; April 2008.
53 Orphenadrine. online.factsandcomparisons.com. Accessed on November 28, 2012.
54 Aspirin, online.factsandcomparisons.com. Accessed on November 28, 2012.
55 Soma Compound with Codeine. Somerset, NJ; Meda Pharmaceuticals; October 2009.
56 Zanaflex [package insert]. Hawthorne, NY; Acorda Therapeutics; April 2008.
57 Flexeril [package insert]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/017821s045lbl.pdf. Accessed on November 30, 2012.
58 Soma [package insert]. Somerset, NJ; Meda Pharmaceuticals; October 2009.
59 Lioresal [package insert]. East Hanover, NJ; Novartis; April 1998.
60 Robaxin [package insert]. Milwaukee, WI; Schwarz Pharma; February 2003.
61 Zanaflex [package insert]. Hawthorne, NY; Acorda Therapeutics; April 2008.
62 Lioresal [package insert]. East Hanover, NJ; Novartis; April 1998.
63 Soma [package insert]. Somerset, NJ; MedPointe Pharmaceuticals; September 2007.
64 Carisoprodol with aspirin, http://www.medicinenet.com/carisoprodol_waspirin-oral/article.htm. Accessed on November 30, 2012.

65 Parafon forte [package insert].Raritan, NJ; Ortho McNeil; August 2000.
66 Lorzone [package insert]. Sayreville NJ; Vertical Pharma; October 2010.
67 Flexeril [package insert]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/017821s045lbl.pdf. Accessed on November 30, 2012.
68 Fexmid. [package insert]. San Diego, CA; Victory Pharmaceuticals; October 2007.
69 Amrix [package insert]. Frazer, PA; Cephalon; December 2008.
70 Dantrium [package insert]. Rochester, MI; JHP Pharmaceuticals; August 2008.
71 Skelaxin [package insert]. Bristol, TN; King Pharmaceuticals; April 2008.
72 Robaxin [package insert]. Milwaukee, WI; Schwarz Pharma; February 2003.
73 Orphenadrine. online.factsandcomparisons.com. Accessed on November 28, 2012.
74 Orphenadrine compound. online.factsandcomparisons.com. Accessed on November 28, 2012.
75 Zanaflex [package insert]. Hawthorne, NY; Acorda Therapeutics; April 2008.
76 Zanaflex [package insert]. Hawthorne, NY; Acorda Therapeutics; April 2008.
77 Clinical Pharmacology. http://www.clinicalpharmacology-ip.com/Default.aspx. Accessed on November 30, 2012.
78 Soma [package insert]. Somerset, NJ; Meda Pharmaceuticals; October 2009.
79 Robaxin [package insert]. Milwaukee, WI; Schwarz Pharma; February 2003.
80 Flexeril [package insert]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/017821s045lbl.pdf. Accessed on November 30, 2012.
81 Fexmid. [package insert]. San Diego, CA; Victory Pharmaceuticals; October 2007.
82 Lioresal [package insert]. East Hanover, NJ; Novartis; April 1998.
83 Skelaxin [package insert]. Bristol, TN; King Pharmaceuticals; April 2008.
84 Dantrium [package insert]. Rochester, MI; JHP Pharmaceuticals; August 2008.
85 Zanaflex [package insert]. Hawthorne, NY; Acorda Therapeutics; April 2008.
86 Aspirin, online.factsandcomparisons.com. Accessed on November 28, 2012.
87 Amrix [package insert]. Frazer, PA; Cephalon; December 2008.
88 Parafon forte [package insert].Raritan, NJ; Ortho McNeil; August 2000.
89 Orphenadrine. online.factsandcomparisons.com. Accessed on November 28, 2012.
90 Skelaxin [package insert]. Bristol, TN; King Pharmaceuticals; April 2008.
91 Lioresal [package insert]. East Hanover, NJ; Novartis; April 1998.
92 Soma [package insert]. Somerset, NJ; Meda Pharmaceuticals; October 2009.
93 Carisoprodol with aspirin, http://www.medicinenet.com/carisoprodol_waspirin-oral/article.htm. Accessed on November 30, 2012.
94 Parafon forte [package insert].Raritan, NJ; Ortho McNeil; August 2000.
95 Lorzone [package insert]. Sayreville NJ; Vertical Pharma; October 2010.
96 Flexeril [package insert]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/017821s045lbl.pdf. Accessed on November 30, 2012.
97 Fexmid. [package insert]. San Diego, CA; Victory Pharmaceuticals; October 2007.
98 Amrix [package insert]. Frazer, PA; Cephalon; December 2008.
99 Dantrium [package insert]. Rochester, MI; JHP Pharmaceuticals; August 2008.
100 Skelaxin [package insert]. Bristol, TN; King Pharmaceuticals; April 2008.
101 Robaxin [package insert]. Milwaukee, WI; Schwarz Pharma; February 2003.
102 Orphenadrine. online.factsandcomparisons.com. Accessed on November 28, 2012.
103 Orphenadrine compound. online.factsandcomparisons.com. Accessed on November 28, 2012.
104 Zanaflex [package insert]. Hawthorne, NY; Acorda Therapeutics; April 2008.
105 Gracies JM, Nance P, Elovic E, et al. Traditional pharmacological treatments for spasticity. Part II: General and regional treatments. Muscle Nerve Suppl. 1997; 6:S92-S120.
106 Stien R, Nordal HJ, Oftedal SI, et al. The treatment of spasticity in multiple sclerosis: a double-blind clinical trial of a new anti-spastic drug tizanidine compared with baclofen. Acta Neurol Scand. 1987; 75(3):190-4.
107 Eyssette M, Rohmer F, Serratrice G, et al. Multi-centre, double-blind trial of a novel antispastic agent, tizanidine, in spasticity associated with multiple sclerosis. Curr Med Res Opin. 1988; 10(10):699-708.
108 Medici M, Pebei M, Ciblis D. A double-blind, long-term study of tizanidine ('Sirdalud') in spasticity due to cerebrovascular lesions. Curr Med Res Opin. 1989; 11(6):398-407.
109 Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manage. 2004; 28(2):140-75.